

IMPACTS OF CRITERIA AIR POLLUTANTS ON THE RESPIRATORY HEALTH OF CHILDREN

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DR. BALMES: I too was given a title I'm not really happy with -- (laughter) -- it's

something about the impacts of criteria pollutants on the developing lung. And, in fact, I don't think there's that much known about the impact of criteria pollutants on the developing lung. The speakers following me probably know more than anybody in that regard does, so I'll let them address that topic.

I was going to talk about, what's known about criteria pollutants and respiratory health of children.

We'll start out with a picture of L.A. smog. I used to live near this area. And most of the criteria pollutants that I'm going to talk about today are depicted in this picture. Certainly there would be ozone, oxides of nitrogen and particulate matter. L.A. doesn't have much in the way of sulfur oxide but I will talk some about SO₂ during my presentation.

CRITERIA POLLUTANTS

- **Ozone**
 - **Oxides of Nitrogen**
 - **Sulfur Oxides**
 - **Particulate Matter**
 - **Carbon Monoxide**
 - **Lead**
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For those of you who are not air pollution pros, the criteria pollutants are those for which the federal EPA has determined that there's an adequate scientific database with regard to epidemiologic studies, controlled human exposure studies, and toxicological studies to stipulate there is a health effect for which we need to control air quality.

There are six of these; I'm going to talk about the first four. Not to say that carbon monoxide and lead aren't important, they're very important, but not particularly with regard to respiratory health, though there may be some debate about carbon monoxide.

There is increasing evidence that carbon monoxide is a reasonable marker for some respiratory health outcomes, maybe a marker for whatever is in the pollutant mix that is responsible for certain health effects.

But what we know most about children with regard to criteria pollutants and health, respiratory health, comes from research into ozone, oxides of nitrogen, sulfur dioxide and particulate matter, so that's what I'm going to talk about.

INCREASED EXPOSURE OF CHILDREN

- **Children spend more time outdoors and are more active (higher ventilation rates).**
 - **Children tend to spend more time outside in the afternoons during summer months when ozone levels are high.**
 - **Children are less likely to report exposure-related symptoms.**
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And a little bit about children and why they're different from adults. I think most of you in this room know these points, but it's probably useful to spend a little time on them.

Children spend more time outdoors on the average and are more active, i.e.; they have higher minute ventilation rates, so they breathe in more air relative to their size than adults do.

Children also tend to spend more time outside in the afternoons during the summer months when certainly ozone levels are high, but often oxides of nitrogen and particulate matter are high as well. In the East Coast sulfur dioxide as well.

And there are also data to suggest that children are less likely to report exposure-related symptoms. So, they may not avoid air pollutant exposure as much as adults.

INCREASED SUSCEPTIBILITY OF CHILDREN

- **Children's lungs may be more susceptible to pollutant-induced injury.**
 - **Oxidant-induced injury may induce inflammation/repair mechanisms that could potentially result in permanent alterations in lung structure.**
 - **Pollutant exposures may result in decreased lung growth/max. lung size.**
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Children also probably have increased susceptibility to criteria pollutants. Ira gave you some theoretical framework for that. But I think it's probably safe to say that children's lungs may be more susceptible to pollutant-induced injury. Oxidant-induced injury in particular may induce inflammation and injury repair mechanisms that could potentially result in permanent alterations in lung structure.

Pollutant exposures may result in decreased lung growth or maximal lung size. And actually, maximal lung size, if it is lower than expected for an individual may be a risk factor for a chronic respiratory disease in adulthood. So, smaller lungs appear to predispose to chronic respiratory disease in adulthood.

CRITERIA POLLUTANTS: ACUTE RESPIRATORY EFFECTS

- **Increased respiratory symptoms**
 - **Increased lower respiratory illness**
 - **Asthma exacerbation**
 - **Reversible lung function decrements**
 - **Airway inflammation**
 - **Altered host defense**
 - **Enhanced allergic responses**
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I think Ira gave you a list of some acute respiratory effects that actually is pretty similar to this one with regard to criteria pollutants. You could have increased respiratory symptoms from exposure to a pollutant, increased lower respiratory illness, asthma exacerbation. You could have reversible lung function decrements; we typically see this with ozone. You could have airway inflammation, either reversible or not, altered host defense in terms of predisposition to infections, and enhanced allergic responses similar to what Ira was talking about with diesel exhaust.

CRITERIA POLLUTANTS: CHRONIC RESPIRATORY EFFECTS

- **Decreased lung growth**
 - **Altered lung structural development (e.g., airway remodeling, “bronchiolarization” of alveolar ducts)**
 - **Increased lifetime risk for asthma, chronic obstructive disease, and lung cancer**
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You could also have chronic respiratory effects. I've mentioned decreased lung growth.

You could have altered lung structural development, airway remodeling. And you could have bronchiolarization of alveolar ducts. Alveolar ducts are really the area of the terminal lung unit where gas exchange starts, it's the junction between the conducting airways and the gas exchange part of the respiratory tract. This term bronchiolarization refers to distal movement of conducting airways, bronchial-type epithelium into what normally would be the gas exchange area. This has been seen in animals with chronic ozone exposure.

Increased lifetime risk for asthma, chronic obstructive lung disease and lung cancer are also chronic respiratory effects, potentially, that could arise from criteria pollutant exposure.

Those of you who have seen my talks on the health effects of air pollutants have seen this slide before; it's one of my favorites, given to me by David Bates. These are rosebushes from identical seeds. This is a rosebush that was grown in filtered L.A. air, and this is the same rosebush grown in smoggy air. And if ozone can do this to a rosebush what can it do to the lungs. And actually, parenthetically, millions of dollars of costs are incurred every year in California from agricultural damage from air pollution.

MECHANISMS OF OZONE TOXICITY

- **Direct oxidation**
 - **Free radical formation**
 - **Lipid peroxidation**
 - **Secondary inflammation/repair**
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Ozone is an oxidant compound that directly causes injury to cells. It basically chemically burns cells, including those of the airway. It generates free radicals, which cause further damage. Macromolecules can be damaged -- here I mention lipids are peroxidized.

And it's not just the direct damage from ozone; there's also the inflammatory response.

You know white blood cells being drawn into the lung may be a good thing when you're trying to fight infection. It may not be a good thing after inhaling a pollutant, because the inflammatory process can cause injury. White blood cells generate free radicals and other oxidant compounds, and whether repair is detrimental or not long-term is always an issue.

OZONE

- **Increased respiratory symptoms and decreases in lung function associated with ozone exposures have been documented in multiple studies of children.**
 - **Panel studies of children with asthma have shown increased symptoms and medication use and decreased peak flow in association with ozone exposure.**
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This slide was to indicate that we know a fair amount about health effects of ozone.

Increased respiratory symptoms and decreases in lung function have been documented in kids exposed to ozone in multiple studies. So you can take kids in summer camp, kids exercising outdoors, and show that they have acute drops in lung function across an exposure.

OZONE

•Multiple studies have documented increased ER visits for asthma in association with high ozone levels.

There have also been panel studies of kids with asthma, and you can show from various markers of asthma exacerbation, that kids will have increased symptoms, increased bronchodilator medication use with ozone exposure.

OZONE AND ASTHMA

CONTROLLED HUMAN EXPOSURES

- **Most studies have not shown asthmatic subjects to be more “sensitive” in terms of lung function responses.**
- **Several studies have shown an enhanced airway inflammatory response. Several studies have shown an enhanced bronchoconstrictor response to allergen.**

I do controlled human exposure studies. There haven't been controlled ozone exposure studies of kids with asthma. Most of the studies have been out in the real world, i.e. summer camps, primarily for ethical reasons. But controlled exposure studies of adults have not really shown asthmatic subjects to be more sensitive in terms of the acute lung function changes.

But what studies have shown is that asthmatics have an enhanced airway inflammatory response to ozone. So ozone causes acute airway inflammation. Asthmatics have underlying airway inflammation. It makes some sense in their data to that asthmatics have an enhanced inflammatory response to ozone.

There are also several studies that have shown an enhanced asthmatic response to allergens after exposure to ozone. So if you expose somebody to ozone who has allergic asthma, and then expose them to the allergen that they respond to, such as some pollen or house dust mite, they have an enhanced response to that allergen.

OZONE AND ASTHMA

WHAT WE DON'T KNOW

- **What is the mechanism of ozone-associated asthma exacerbation?**
 - **What is the mechanism of ozone enhancement of response to allergen?**
 - **What is the relative importance of exposure to ambient ozone as a trigger for asthma exacerbation?**
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So what don't we know about ozone and asthma?

Well, we don't know the mechanism of ozone-associated asthma exacerbation. There are good epidemiologic data to show that individuals with asthma have greater risk of exacerbation, greater risk of going to an emergency room for treatment of an exacerbation with high ozone days, but we don't understand the mechanism of this.

It may have something to do with this enhanced airway inflammatory response, it may have something to do with the enhanced response to allergen, but we really don't know. And we don't know the mechanism of ozone enhancement of response to allergen.

You'll see ozone isn't the only criteria pollutant that has this effect.

And we really don't know the relative importance of exposure to ozone as a trigger for asthma exacerbation. We know that ozone is something that can be associated with asthma exacerbation, but we don't know its relative importance compared to other pollutants or compared to other exposures.

OZONE AND ASTHMA

WHAT WE DON'T KNOW

- **What is the effect of childhood exposure to ozone on the subsequent course of asthma?**
 - **Is there a subset of asthmatic persons at particular risk for ozone-induced asthma exacerbation? If so, are there specific genetic determinants of this risk?**
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We also don't know the effect of childhood exposure to ozone on the subsequent course of asthma. We know that asthmatics have acute responses to criteria pollutants but we don't know how that impacts on how they do over the long haul.

And we have reason to suspect, but we really don't know how to define that there's a subset of asthmatic persons at particular risk for responses to ozone. And if there is such a subset, are there specific genetic determinants of this risk?

And Ira didn't get a chance to mention this, it wasn't specifically germane to his topic, but there is a large study of which he is the P.I. of the health component, the Fresno Asthmatic Children's Environment Study (FACES), which is hoping to address this question: What is the effect of acute responses to ozone and other pollutants in asthmatics over the long-term course?

OZONE

- **Decreased flow rates at mid and low lung volumes (“small airways dysfunction”) have been found in college students in association with lifetime exposure to ozone (Kunzli et al.).**
 - **Decreased flow rates have also been associated with >4 years of residence in a high ozone area (Galizia and Kinney).**
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What are the chronic effects of ozone on kids? There are some data that suggest that decreased flow rates at mid and low-lung volumes, so-called small airways dysfunction, can be found in college students in association with lifetime exposure to ozone. There are two studies that have found this association.

The first, a pilot study of U.C. Berkeley freshmen by Nino Kinzlo, Ira Tager, and myself involved those that grew up in Southern California prior to coming to Berkeley, and those that grew up in Northern California with putatively less exposure to ozone and other pollutants. There was a difference in lung function in these small-airways parameters between the Southern California and Northern California kids. We're currently trying to redo that study to see if we find the same result.

And there's a somewhat parallel study by Pat Kinney and colleagues taking Yale College students from all over the country, not just from California, and looking at flow rates and where they had lived in the past. And if they'd lived at least four years in a high-ozone area they had decreased flow rates compared to people who had not lived four years in such a high-ozone area.

So, there are some data to suggest that ozone exposure in childhood may have chronic effects on adult lung function.

OXIDES OF NITROGEN

- **NO₂ not as potent of an oxidant as ozone**
 - **NO₂ reacts with H₂O to form HNO₃**
 - **? NO₂-ozone interaction**
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This is a slide introducing nitrogen dioxide, which is another oxidant pollutant found in association with ozone, it's actually a precursor for ozone. It's less potent of an oxidant than ozone. And I think I also mentioned that when it's inhaled into the airway which is a humid environment it generates nitric acid.

OXIDES OF NITROGEN

- **Increased risk of lower respiratory illness in children associated with indoor exposures to oxides of nitrogen**
 - **Increased risk of both bacterial and viral experimental infections in NO₂-exposed animals**
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This is an old slide to remind me to say that in addition to being an outdoor pollutant NO₂ also has indoor sources such as gas stoves and heaters, and there may be greater exposure indoors than outdoors depending on where you live.

NO₂ AND ASTHMA

CONTROLLED HUMAN EXPOSURES

- **Inconsistent dose-response re: increased airway responsiveness**
 - **Less airway inflammation than with ozone in normal subjects**
 - **Several studies have shown an enhanced bronchoconstrictor response to allergen**
-

So what do we know about oxides of nitrogen and respiratory health effects?

There are a lot of data, mostly positive, some negative, but if you take a meta-analysis of all the extant data with regard to indoor exposure of kids to oxides of nitrogen and risk of lower respiratory illness there does appear to be an increased risk.

There are also data from animal models of infection to suggest that NO₂-exposed animals have an increased risk of both bacterial and viral infections. And, so this epidemiologic data in kids is supported to some extent by experimental animal data.

NO₂ AND ASTHMA

EPIDEMIOLOGICAL STUDIES

- **Limited data suggest that high-level exposure may cause acute decrements in peak expiratory flow.**
 - **Recent data from the So. Cal. Children's study have shown associations between exposure and LRS in children with asthma.**
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How about NO₂ and asthma?

There are limited data to suggest that high-level exposure may cause acute decrements and peak expiratory flow. That's not too exciting.

OXIDES OF NITROGEN

•Decreased rate of growth in forced vital capacity in association with NO₂ exposure observed longitudinally in South California Children's Health Study.

But, recent data from the Southern California Children's Health Study, the ARB-USC study have increased interest in NO₂ and its effects on asthmatic children. The main purpose of the study is to look at the effect of criteria pollutants and atmospheric acidity on growth of lung function, that growth that Ira showed you from early childhood to young adulthood. And there are data from that study which have shown associations

between exposures to oxides of nitrogen and lower respiratory symptoms in children with asthma. Rob McConnell is the first author on a recent paper published in "Environmental Health Perspectives," in which these data were reported.

In terms of controlled human exposure studies with regard to NO₂ and asthma, NO₂ causes less airway inflammation than ozone in adult subjects without asthma. And the data with adult asthmatics are sort of all over the place, so not worth going into detail on. Like I showed you for ozone, several studies, about four now, have shown an enhanced bronchoconstrictor response to allergen after NO₂ exposure. So here's another oxidant pollutant that appears capable of enhancing allergic responses to a specific allergen.

What don't we know about NO₂ in asthma? Well, just like for ozone, we don't know the mechanism of NO₂ enhancement of response to allergen. And with regard to the increased bronchitic systems of asthmatic kids in the Southern California Children's Health Study, we don't know if NO₂ is merely a surrogate for some other factors, i.e., the traffic-pollution mix.

How about chronic effects? Well, the main purpose of the Southern California Children's Health Study was to look at growth of lung function, whether that was impaired at all, and the pollutant with the strongest effect so far on decreasing the rate of growth of lung function was NO₂. The longitudinal data haven't actually been published yet, but they've been presented, and NO₂ is the pollutant with the greatest effect.

SULFUR DIOXIDE

- **The NAAQS for SO₂ allows for relatively high short-term peak exposures.**
 - **People with asthma are not protected from exacerbation caused by brief exposures.**
-

Moving on to sulfur dioxide, the national ambient air quality standard for sulfur dioxide is a 24-hour mean and the shortest averaging time is for three hours. That basically means that people with asthma are not felt by the federal EPA to be at risk for exacerbation for brief exposures. This, despite the fact that multiple studies of adults have shown that sulfur dioxide at relatively low concentrations for relatively short exposure durations can cause acute bronchospasm.

SULFUR DIOXIDE

- **Sulfur dioxide can induce acute bronchospasm in asthmatic children at relatively low concentrations and short exposure durations.**
 - **Several studies have shown associations between SO₂ exposure and decreased forced vital capacity.**
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So I think I can safely say that sulfur dioxide peak exposures such as kids might get downwind from a refinery, which wouldn't violate the current federal standard, could in fact cause acute bronchospasm, enough for kids to have to use medication.

Several studies have shown associations between sulfur dioxide exposure and decreased forced vital capacity, how much air you can blow out with no time limit. Now these studies have been from places like Poland and China, where SO₂ has been measured.

There're certainly other pollutants involved in these exposures. But in any event, there was an association with SO₂, whether it's an SO₂ effect or just SO₂ as a surrogate for the effect of the pollutant mix.

PARTICULATE MATTER

- **Several studies have documented increased respiratory symptoms or increased hospitalizations for acute respiratory illness in children in association with PM exposures.**
 - **Decreased peak flow has been observed in panels of normal and asthmatic children in association with PM10.**
-

The final pollutant I want to talk about is particulate matter, which is a mixture, unlike the three gases I've talked about so far it's a *gemisch* of things. It's solid and liquid particles, particles of biological origin, fungal spores, pollens, endotoxins, and the particles are of varying size.

The size of the particles that has been of importance to EPA with regard to the ambient air quality standard has changed over time. It was initially total suspended particulate; it's currently PM-10, so particulate matter of 10 microns aerodynamic diameter or less. And the proposed new standard would have a component for PM-2.5 or fine particulate. This is interesting to a California audience in that the EPA decided to go to a PM-2.5 standard because they felt that the data, the epidemiologic data were strongest for health effects in fine particles, and fine particles primarily come from combustion sources. But there are data showing that the coarse fraction between 10 and 2.5, which is mostly crustal materials (i.e., from the Earth's crust) of geologic origin, also have health effects. In California, as opposed to the East Coast, a lot of our PM is of this coarse fraction size. I am one who believes that the data are not sufficient to sort of ignore the coarse fraction and focus all of our attention on 2.5.

Here's a slide showing a source of PM, this is a paper and pulp mill, obvious plume of smoke. But this next slide shows the Owens Lake, across the Sierra from the Central Valley. This is an area where some of the highest particulate exposures in the state occur

when there are windstorms over the dry lakebed of Owens Lake. For those of you who don't know California history, Los Angeles drained this lake dry a number of years ago.

PM AND ASTHMA

DIESEL EXHAUST PARTICULATE

- **Induces airway inflammation in normal subjects.**
 - **Enhances local allergic responses after nasal instillation in humans.**
 - **Induces airway responsiveness in mice; enhances lower airway responses to allergen in mice.**
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Several studies have documented increased respiratory symptoms or increased hospitalizations for acute respiratory illness in kids exposed to PM, or an association with PM exposures like has been observed for ozone. Decreased peak flow has been observed in panels of normal and asthmatic children in association with PM-10.

Then there's a particular type of PM, diesel exhaust particulate that Ira's already talked about. Diesel exhaust particulate has been shown to induce airway inflammation in normal adult subjects. There was a study done by Thomas Sandstrom and colleagues in Sweden. Exposures were higher than what would occur with ambient exposures, but only about an order of magnitude higher than high ambient exposures. So diesel exhaust particulate appears to be capable of causing airway inflammation.

The data about local allergic responses being enhanced come from human data. It's not just animal data. The UCLA group, with Andy Saxton, David Diaz-Sanchez, has instilled diesel exhaust particulate into allergic rhinitic humans and shown enhanced allergic responses. And there are abundant animal data, primarily in mice, to show that you get enhanced lower airway responses to allergen in sensitized mice, and that diesel exhaust particulate appears to be an adjuvant for actually increasing sensitization of animals

PM AND ASTHMA

WHAT WE DON'T KNOW

- **What is the relative importance of exposure to ambient PM as a trigger for asthma exacerbation?**
 - **What is the component(s) of PM that acts as a trigger for asthma exacerbation?**
 - **What is the mechanism of DEP enhancement of response to allergen?**
-

So what don't we know about PM in asthma? Again, we don't know the relative importance of exposure to ambient PM as a trigger for asthma exacerbation. As for ozone, we know that you can find associations between PM exposure and asthma exacerbation but we don't know if it's a very small effect or not. As I should have said for ozone, even if it is a relatively small effect, since most asthmatics in polluted areas will be exposed to PM, the actual public health impact could be high even if it's a small effect.

We don't know the components of PM that act as a trigger for asthma exacerbation. There's currently a lot of interest in diesel exhaust particulate, but there may be other components as well. And again, we don't know the mechanism of diesel exhaust particulate enhancement of response to allergen, but we're probably closer to finding that out with diesel exhaust than with ozone or NO₂.

PM AND ASTHMA

WHAT WE DON'T KNOW

- **What is the effect of childhood exposure to PM on the subsequent course of asthma?**
 - **Is there a subset of asthmatic persons at particular risk for PM-induced asthma exacerbation? If so, are there specific genetic determinants of this risk?**
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Parallel to what I said for ozone, we don't know the effect of acute responses of asthmatic kids to childhood exposures to PM on the subsequent course of their asthma. And again we don't know what subsets of kids are at risk and the genetic determinants of this risk.

PARTICULATE MATTER

- **Decreased rate of growth in forced vital capacity in association with PM10 exposure observed longitudinally in South California Children's Health Study.**
 - **Decreased rate of growth of forced vital capacity in Cracow children living in polluted areas (PM and SO₂ exposures).**
-

In terms of chronic effects, the Southern California Children's Health Study has shown a decreased rate of growth in forced vital capacity in association with PM-10 as well as NO₂. And there was one study of kids in Cracow, Poland living in polluted areas where there were both PM and SO₂ exposures which showed decreased rate of growth of lung function compared to kids living in less polluted areas. So there's reason to believe that PM may affect growth of lung function.

TRAFFIC

- **Several studies have shown increased respiratory symptoms in children living near roadways with increased traffic density.**
 - **Several studies have shown increased asthma prevalence in relation to traffic exposure (with NO₂ often showing the best single pollutant correlations).**
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There are a number of studies which haven't focused on exposure to specific pollutants but rather on exposure to traffic; there's a lot of interest in this right now epidemiologically. Several studies have shown increased respiratory symptoms in children living near roadways with increased traffic density. There are actually some lung function data as well. And several studies have shown increased asthma prevalence in relation to traffic exposure, with NO₂ often being the pollutant with the best correlations in this regard.

OTHER FACTORS

- **Dietary intake of antioxidants may play an important role in modifying the effects of air pollutants.**
 - **Genetic differences in function of oxidant and antioxidant enzymes, cytokines, and other proteins involved in modulating injury, inflammation, and repair are likely to be of critical importance.**
-

There are other factors that may modify the response of kids to air pollutants. Dietary intake of antioxidants is likely to play a role and there are increasing data in this regard with regard to adults and the effects of air pollutants. Genetic differences in the function of a number of relevant proteins are probably also involved in modulating injury. There are differences in response to pollutants in various strains of mice for example. And it's likely that polymorphisms in oxidant enzymes, antioxidant enzymes, various cytokines, and related proteins are likely to be of importance to the response. And, hopefully, further elaboration of these genetic differences will help us understand the heterogeneity in response to pollutants over time.

KEY QUESTIONS

- **Time periods in development**
 - **Critical points re: later life impacts**
 - **Identification of susceptible children**
 - **Interactions**
 - **Adequacy of animal models**
 - **Important data gaps**
 - **Improvement in risk assessment**
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The key questions that the speakers in this workshop were asked to deal with include what are the critical time periods in terms of development, and what are the critical points with regard to later-life impacts. I think that it's likely that in utero exposures to pollutants may have some impact, there are insufficient data at the present time.

What are the critical points regarding later-life impacts. As Ira pointed out, exposures in the first couple years of life are likely to have the greatest effect on the airways development, but some later exposures will decrease maximal growth of lung size.

Identification of susceptible children. What we know from numerous epidemiologic studies is that asthmatic kids appear to be more susceptible, asthmatic kids that are symptomatic and are requiring more medication appear to be more susceptible, but we don't know much more than that. Hopefully we'll have some genetic markers soon.

Certainly interactions are important, you know, rarely do people get exposed to single pollutants, it's almost always a mixture, and it's likely that exposure to ozone and other oxidant pollutants and particulate at the same time will have different effects than single exposures, single pollutant exposures. There are interactions with other things like environmental tobacco smoke that are likely to be important, allergen exposure.

Adequacy of animal models. I think we've had good animal models for acute and chronic effects of various -- of the criteria pollutants, but we haven't spent as much time on development, especially in utero exposures. And again, Kent Pinkerton will be talking about that I'm sure.

The important data gaps are the next few slides.

IMPORTANT DATA GAPS

- **Whether childhood exposure to air pollution causes chronic respiratory dysfunction/impairment remains unclear.**
 - **If so, what are the independent and joint effects of specific pollutants?**
 - **If so, who are the susceptible children?**
 - **If so, what are the mechanisms?**
-

I don't have a clue about how to improve risk assessment at this point with regard to the criteria pollutants in respiratory health, other than we need more data.

Some of the data gaps that I think are most important. Whether childhood exposure causes chronic respiratory dysfunction or impairment remains unclear. There are some suggestions. The Southern California children's study hopefully will give us our best data in this regard, but I think it remains unclear.

IMPORTANT DATA GAPS

- **Whether exposure to outdoor air pollutants increases the risk of development of asthma is not known.**
- **If so, what are the specific pollutants and interactions of interest? Who is susceptible? What are the mechanisms?**

IMPORTANT DATA GAPS

- **Whether acute responses to outdoor air pollutants affect the course and severity of asthma is unknown?**
 - **What are the mechanisms by which outdoor air pollutants enhance allergic responses?**
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If there are chronic effects what are the independent and joint effects of specific pollutants? If so, who are the susceptible children? If so, what are the mechanisms?

And I think we might be able to regulate, might be able to do risk assessment and regulate without understanding biological mechanism, but we'll do a better job in terms of prevention and control if we understand biological mechanism.

Whether exposure to outdoor pollutants increases the risk of development of asthma is not really known. I think there's relative consensus that asthma can be exacerbated by criteria pollutants, but there's not consensus that there's increased risk of developing asthma with criteria pollutant exposure. And, you know that would be a nice study to do; it probably would be difficult, I think you really need an inception cohort type of study, and it might need to be across multiple cities in terms of multiple types of pollutant profiles. But I think it would be nice to answer this question once and for all.

If the criteria pollutants increase the risk of development of asthma then we need to know

which specific pollutants, which interactions of interest, the susceptible subgroup and mechanism.

Whether acute responses to criteria pollutants affect the course and severity of asthma is, again, unknown. Those of us involved with the Fresno children's environment study, we're trying to address this issue; hopefully we'll have some data for you in a few years. And if in fact acute responses are related to the course of asthma, we need to understand the mechanisms. And the Fresno asthmatic children's study is set up to try to actually address epidemiologically some potential information with regard to mechanism.

And I think that's my last slide. So thanks for your attention. (Applause.)

DR. MARTY: Questions for Dr. Balmes? We'll take a couple questions.

DR. ALEXEFF: Yeah, George Alexeff, I have a question.

Do you have a sense quantitatively of the differences between the results in the controlled human studies and the summer camp-type studies in children? In other words, does it appear that children are -- how predictive are the human adult controlled studies for the concentrations that are affecting kids in summer camps?

DR. BALMES: Yeah, you probably know these data and that's why you're asking me, but it's a good question, because that has been looked at. And in general the dose response from the summer camps and the outdoor exposure is actually steeper than in controlled human exposure studies. So, again, that's a real-world exposure versus pure ozone exposure. So the real-world exposure, which is probably involving -- not probably, is involving exposure to other things including PM seems to have a steeper slope than the controlled exposure studies, suggesting that interactions are important.